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(54) Title: BIPHENYLAMIDE DERIVATIVES AS $5HT_{1D}$ ANTAGONISTS

(57) Abstract

Novel biphenyl amide derivatives as $5HT_{1D}$ antagonists, processes for their preparation, pharmaceutical compositions containing them and their use for the treatment of CNS disorders.

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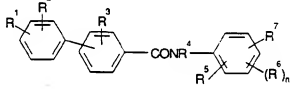
BIPHENYLAMIDE DERIVATIVES AS 5HT1D ANTAGONISTS

The present invention relates to novel amide derivatives, processes for their preparation, and pharmaceutical compositions containing them.

EPA 0 533 266/7/8 disclose a series of benzanilide derivatives which are said to possess $5HT_{1D}$ receptor antagonist activity. These compounds are said to be of use in the treatment of various CNS disorders.

A structurally distinct class of compounds have now been discovered and have been found to exhibit $5HT_{1D}$ receptor antagonist activity. In a first aspect, the present invention therefore provides a compound of formula (I) or a salt or N-oxide thereof:



(I)

in which

R^1 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, acyl, nitro, trifluoromethyl, cyano, SR^9, SOR^9, SO_2R^9, $SO_2NR^{10}R^{11}$, CO_2R^{10}, $NR^{10}SO_2R^{11}$, $CONR^{10}R^{11}$, $CO_2NR^{10}R^{11}$, $CONR^{10}(CH_2)_aCO_2R^{11}$, $(CH_2)_aNR^{10}R^{11}$, $(CH_2)_aCONR^{10}R^{11}$, $(CH_2)_aNR^{10}COR^{11}$, $(CH_2)_aCO_2C_{1-6}$alkyl, $CO_2(CH_2)_aOR^{10}$, $CONHNR^{10}R^{11}$, $NR^{10}R^{11}$, $NR^{10}CO_2R^{11}$, $NR^{10}CO(CH_2)_aNR^{10}R^{11}$, $NR^{10}CONR^{10}R^{11}$, $CR^{10}{=}NOR^{11}$, $CNR^{10}{=}NOR^{11}$, where R^9, R^{10} and R^{11} are independently hydrogen or C_{1-6}alkyl and a is 1 to 4 or R^1 is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur;

R^2 and R^3 are independently hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, C_{1-6}alkylOC_{1-6}alkyl, acyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano, CO_2R^{10}, $CONR^{10}R^{11}$, $NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen or C_{1-6}alkyl;

R^4 is hydrogen or C_{1-6}alkyl and R^5 is hydrogen, halogen, hydroxy, C_{1-6}alkyl or

C_{1-6}alkoxy or R^4 and R^5 together form a group -A- where A is $(CR^{12}R^{13})_q$ where q is 2, 3 or 4 and R^{12} and R^{13} are independently hydrogen or C_{1-6}alkyl or A is $(CR^{12}R^{13})_r$-D where r is 0, 1, 2 or 3 and D is oxygen, sulphur or $CR^{12}=CR^{13}$;

R^6 is hydrogen, halogen, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy;

n is 1 or 2; and

R^7 is an optionally substituted 5 to 7-membered saturated or partially saturated heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen or sulphur or R^7 is an optionally substituted 6,6 or 6,5 bicyclic ring containing a nitrogen atom and optionally a further heteroatom selected from from oxygen, nitrogen or sulphur.

C_{1-6}alkyl groups, whether alone or as part of another group, may be straight chain or branched.

Suitably R^1 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, acyl, nitro, trifluoromethyl, cyano, SR^9, SOR^9, SO_2R^9, $SO_2NR^{10}R^{11}$, CO_2R^{10}, $NR^{10}SO_2R^{11}$, $CONR^{10}R^{11}$, $CO_2NR^{10}R^{11}$, $CONR^{10}(CH_2)_aCO_2R^{11}$, $(CH_2)_aNR^{10}R^{11}$, $(CH_2)_aCONR^{10}R^{11}$, $(CH_2)_aNR^{10}COR^{11}$, $(CH_2)_aCO_2C_{1-6}$alkyl, $CO_2(CH_2)_aOR^{10}$, $CONHNR^{10}R^{11}$, $NR^{10}R^{11}$, $NR^{10}CO_2R^{11}$, $NR^{10}CO(CH_2)_aNR^{10}R^{11}$, $NR^{10}CONR^{10}R^{11}$, $CR^{10}=NOR^{11}$, $CNR^{10}=NOR^{11}$, where R^9, R^{10} and R^{11} are independently hydrogen or C_{1-6}alkyl and a is 1 to 4.

When R^1 is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur, suitable heterocyclic rings include thienyl, furyl, pyrrolyl, triazolyl, diazolyl, imidazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyridyl, pyrimidyl and pyrazinyl. The heterocyclic rings can be linked to the remainder of the molecule via a carbon atom or, when present, a nitrogen atom. Preferably R^1 is oxadiazolyl, most preferably a 5-methyl-1,2,4-oxadiazol-3-yl group.

Suitably R^2 and R^3 are independently hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, C_{1-6}alkylOC_{1-6}alkyl, acyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano, CO_2R^{10}, $CONR^{10}R^{11}$, $NR^{10}R^{11}$ where R^{10} and R^{11} are hydrogen or C_{1-6}alkyl. Preferably R^2 is C_{1-6}alkyl, in particular methyl. Preferably R^3 is hydrogen.

Suitably R^4 is hydrogen or C_{1-6}alkyl and R^5 is hydrogen, halogen, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy or R^4 and R^5 together form a group -A- where A is $(CR^{12}R^{13})_q$ where q is 2, 3 or 4 and R^{12} and R^{13} are independently hydrogen or C_{1-6}alkyl or A is $(CR^{12}R^{13})_r$-D where r is 0, 1, 2 or 3 and D is oxygen, sulphur or $CR^{12}=CR^{13}$. Preferably R^4 and R^5 are both hydrogen or R^4 and R^5 are linked to form a group A.

Preferably A is $(CR^{12}R^{13})_q$ where R^{12} and R^{13} are both hydrogen and q is 2 or 3 such that A forms an ethyl or propyl linkage.

Suitably R^6 is hydrogen, halogen, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy. Preferably R^6 is C_{1-6}alkoxy, in particular methoxy. Suitably n is 1 or 2, preferably n is 1.

Suitably R^7 is an optionally substituted 5 to 7-membered saturated or partially saturated heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen or sulphur. Examples of such groups include piperidine and tetrahydropyridine. Alternatively R^7 is a 6,6 or 6,5 bicyclic ring containing a nitrogen atom and optionally a further heteroatom selected from from oxygen, nitrogen or sulphur. Examples of such groups include tropane, isoquinuclidine and granatane rings. Optional substituents for such ring systems include C_{1-6}alkyl, such as methyl. For example, R^7 groups containing a nitrogen atom can be substituted on the nitrogen atom by a methyl group.

The groups R^1, R^2 and R^3 can be attached to their respective rings at any suitable position.

Particularly preferred compounds of the invention include:

N-[4-Methoxy-3-(1-methyl-4-piperidinyl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,

N-[4-Methoxy-3-(4-piperidinyl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,

N-[4-Methoxy-3-(1-methyl-1,2,3,6-tetrahydropyrid-4-yl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,

N-[3-(8-Azabicyclo[3.2.1]octan-3-yl)-4-methoxyphenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,

N-[4-Methoxy-3-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,

[3,4-Dihydro-6-methoxy-7-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-2H-quinolin-1-yl]-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methanone,

[7-(8-Azabicyclo[3.2.1]octan-3-yl)-3,4-dihydro-6-methoxy-2H-quinolin-1-yl]-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methanone,

N-[3-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,

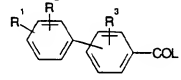
and pharmaceutically acceptable salts thereof.

Preferred salts of the compounds of formula (I) are pharmaceutically acceptable salts. These include acid addition salts such as hydrochlorides, hydrobromides, phosphates, acetates, fumarates, maleates, tartrates, citrates, oxalates, methanesulphonates and p-toluenesulphonates.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and the mixtures thereof including racemates. Tautomers of compounds of formula (I) and mixtures thereof also form an aspect of the invention.

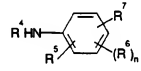
In a further aspect the present invention provides a process for the preparation of a compound of formula (I) which comprises.

(a) for compounds where R^4 is hydrogen or C_{1-6}alkyl and R^5 is hydrogen, halogen, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy, reaction of a compound of formula (II):



(II)

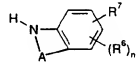
in which R^1, R^2 and R^3 are as defined in formula (I) and L is a leaving group, with a compound of formula (III):



(III)

in which R^4 and R^5 are as defined above and R^6, R^7 and n are as defined in formula (I); or

(b) where R^4 together with R^5 forms a group A, reaction of a compound of formula (II) as defined above with a compound of formula (IV):



(IV)

in which A is as defined above and R^6, R^7 and n are as defined in formula (I);

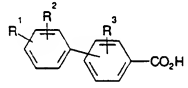
and optionally after (a) or (b) and in any order:

- converting a compound of formula (I) into another compound of formula (I)
- forming a pharmaceutically acceptable salt.

Suitable activated carboxylic acid derivatives of formula (II) include acyl halides and acid anhydrides. Activated compounds of formula (II) can also be prepared by reaction of the corresponding carboxylic acid with a coupling reagent such as carbonyldiimidazole, dicyclohexylcarbodiimide or diphenylphosphorylazide. Preferably the group L is halo, particularly chloro.

Alternatively L is an ester forming group such that the resulting esters of formula (II) can be reacted with compounds of formula (III) in the presence of an organo-aluminium reagent such as trimethylaluminium. Such a reaction is typically carried out in the presence of an inert solvent such as toluene.

A compound of formula (II) is typically reacted with a compound of formula (III) or (IV) in an inert organic solvent such as DMF, THF or dichloromethane at ambient or elevated temperature in the presence of a base such as triethylamine or pyridine. Compounds of formula (II) can be prepared from a compound of formula (V):



(V)

in which R^1, R^2 and R^3 are as defined in formula (I) using standard procedures. For example acid chlorides can be prepared by reaction with phosphorous pentachloride, oxalyl chloride or thionyl chloride. Acid anhydrides can be prepared by reaction with a suitable acid anhydride, for example trifluoroacetic anhydride.

Intermediate compounds of formula (V) are commercially available or can be prepared using standard procedures such as those outlined in EPA 533266/7/8 and GB A 2 276 160. Intermediate compounds of formulae (III) and (IV) can be prepared using standard procedures known in the art. Certain intermediate compounds of formulae (III) and (IV) are novel and form a further aspect of the invention.

It will be appreciated to those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. Standard protection and deprotection techniques can be used. For example, primary amines can be protected as phthalimide, benzyl, benzyloxycarbonyl or trityl derivatives. These groups can be removed by conventional procedures well known in the art.

Carboxylic acid groups can be protected as esters. Aldehyde or ketone groups can be protected as acetals, ketals, thioacetals or thioketals. Deprotection is achieved using standard conditions.

Certain compounds of formula (I) can be converted into further compounds of formula (I) using standard procedures.

$5HT_{1D}$ Antagonists, and in particular the compounds of the present invention, are expected to be of use in the treatment of CNS disorders such as mood disorders, including depression, seasonal effective disorder and dysthymia; anxiety disorders, including generalised anxiety, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder, memory disorders, including dementia, amnestic disorders and age-associated memory impairment; and disorders of eating behaviours, including anorexia nervosa and bulimia nervosa. Other CNS disorders include motor disorders such as Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders.

$5HT_{1D}$ Antagonists, and in particular compounds of the present invention, may also be of use in the treatment of endocrine disorders such as hyperprolactinaemia, in the treatment of vasospasm (particularly in the cerebral vasculature) and hypertension, as well as disorders in the gastrointestinal tract where changes in motility and secretion are involved. They may also be of use in the treatment of sexual dysfunction.

Therefore, the present invention, provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in therapy.

The present invention also provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment of the aforementioned disorders.

In another aspect the invention provides the use of a compound of general formula (I) or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of the aforementioned disorders.

In a further aspect the invention provides a method of treating the aforementioned disorders which comprises administering an effective amount to a patient in need of such treatment of a compound of general formula (I) or a pharmaceutically acceptable salt or solvate thereof.

In particular the invention provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment or prophylaxis of depression.

It will be appreciated by those skilled in the art that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, different antidepressant agents.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

The following example illustrate the invention.

Description 1

1-Carbomethoxy-4-(2-methoxyphenyl)piperidine

1-Methyl-4-(2-methoxyphenyl)piperidine (J. Org. Chem. 1947, 12, 885-93) (3.02g, 14.73 mmol) was dissolved in dichloromethane (100 ml) and was treated with 1-chloroethyl chloroformate (1.07 ml, 19.15 mmol), followed by diisopropylethylamine (2.57 ml, 14.73 mmol) with stirring under argon. After 16 h, the reaction mixture was evaporated under reduced pressure and dissolved in methanol (100 ml). The reaction mixture was then heated to reflux. After 0.5 h, the reaction mixture was allowed to cool, was evaporated under reduced pressure and was dried *in vacuo* to give a buff solid, which was redissolved in dichloromethane (100 ml) and treated with methyl chloroformate (1.14 ml, 14.73 mmol), followed by triethylamine (2.05 ml, 14.73 mmol) with stirring. After 24h the reaction mixture was washed with $NaHCO_3$ solution (1X), water (1X) and 10% citric acid (2X). The organic layer was then dried (Na_2SO_4) and evaporated under reduced pressure to give an orange oil that crystallised on standing. The solid was recrystallised from 60-80 petrol to give the **title compound** as cream coloured crystals (1.05g, 30%).

m.pt 78-79°C

^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.20 (m, 2H), 6.90 (m, 2H), 4.30 (brs, 2H), 3.88 (s, 3H), 3.70 (s, 3H), 3.11 (m, 1H), 2.91 (t, 2H), 1.80 (m, 2H), 1.60 (m, 2H).

Description 2

4-(5-Amino-2-methoxyphenyl)-1-carbomethoxypiperidine

The product from description 1 (0.500g, 2.01 mmol) was dissolved in Ac_2O (30 ml) and was cooled to 0° C. Freshly ground copper (II) nitrate hemipentahydrate (0.561g, 2.41 mmol) was then added slowly (over 5 minutes). The reaction mixture was then allowed to warm to room temperature and was stirred at room temperature for 1h. The reaction mixture was then treated with water (30 ml), stirred for a further 0.5 h and then sodium bicarbonate (solid) was added until pH8 was reached. The resultant blue solution was then extracted with dichloromethane (2X). The combined organic layers were then dried (Na_2SO_4) and evaporated under reduced pressure to give a yellow oil which was dried *in vacuo* (0.501g). The oil was then redissolved in ethanol (40 ml) and was hydrogenated at atmospheric pressure in the presence of 10% PdC (0.05g). After 5h, the reaction mixture was filtered through kieselguhr. The filter pad was washed with EtOH and the filtrate was evaporated under reduced pressure to give a brown oil which was dried *in vacuo*. The oil

was purified by SiO_2 chromatography (Et_2O as eluant) to give the **title compound** as an off white solid (0.150g, 33%).

^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 6.70 (d, 1H), 6.20 (m, 2H), 4.70 (brs, 2H), 3.75 (s, 3H), 3.70 (s, 3H), 3.40 (s, 2H), 3.05 (m, 1H), 2.85 (t, 2H), 1.78 (m, 2H), 1.60 (m, 2H).

Description 3

4-(5-Amino-2-methoxyphenyl)-1-methylpiperidine

The product from description 2 (0.143g, 0.542 mmol) was dissolved in dry THF (10 ml), and was treated with lithium aluminium hydride (0.041g, 1.084 mmol) and was heated to reflux with stirring under argon. After 2h, the reaction mixture was allowed to cool and water (0.041 ml) was added, followed by 10% NaOH (0.063 ml) and water (0.104 ml). The mixture was then stirred at room temperature for 0.5 h, before being filtered through kieselguhr. The filter pad was then washed with dry THF (2X), and the filtrate was evaporated under reduced pressure and dried *in vacuo* to give the **title compound** as a brown oil (0.103g, 86%).

^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 6.68 (d, 1H), 6.58 (d, 1H), 6.50 (dd, 1H), 3.75 (s, 3H), 3.39 (s, 2H), 2.90 (m, 3H), 2.31 (s, 3H), 2.05 (dt, 2H), 1.75 (m, 4H).

Description 4

N-[3-(1-Carbomethoxy-4-piperidinyl)-4-methoxyphenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide

The product from description 2 (0.130g, 0.492 mmol) was transformed to give the **title compound** (0.213g, 85%) as a white foam, according to the method described in example 1.

^1H NMR (250 MHz, $CDCl_3$) δ(ppm): 7.97 (m, 4H), 7.81 (s, 1H), 7.55 (dd, 1H), 7.48 (d, 2H), 7.38 (m, 2H), 6.90 (d, 1H), 4.30 (brs, 2H), 3.85 (s, 3H), 3.70 (s, 3H), 3.12 (m, 1H), 2.88 (t, 2H), 2.70 (s, 3H), 2.30 (s, 3H), 1.82 (m, 2H), 1.62 (m, 2H).

Description 5

N-[3-Bromo-4-methoxyphenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide

4-Methoxy-3-bromoaniline (0.521g, 0.258 mmol) was transformed to give the **title compound** (0.920g, 75%) as a cream solid according to the method outlined in example 1.

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.90 (m, 6H), 7.61 (dd, 1H), 7.48 (d, 2H), 7.35 (d, 1H), 6.90 (d, 1H), 3.90 (s, 3H), 2.70 (s, 3H), 2.30 (s, 3H).

Description 6

N-[3-(4-Pyridyl)-4-methoxyphenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide

The product from description 5 (0.400g, 0.837 mmol) was transformed to give the **title compound** (0.162g, 41%) as an off white solid according to the method outlined in EP 0533 267A1, Intermediate 23.

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 8.62 (d, 2H), 8.10 (s, 1H), 7.97 (m, 4H), 7.67 (m, 2H), 7.50 (m, 4H), 7.31 (d, 1H), 7.03 (d, 1H), 3.85 (s, 3H), 2.70 (s, 3H), 2.30 (s, 3H).

Description 7

3-Hydroxy-3-(2-methoxyphenyl)-8-methyl-8-azabicyclo[3.2.1]octane

A stirred solution of 2-bromoanisole (9.25 ml, 0.074 mol) in dry diethyl ether (110 ml) under argon was cooled to 0° C and was treated with n-butyllithium (1.6M) (45.6 ml, 0.073 mol) slowly. The reaction mixture was then allowed to warm to room temp. After 0.5 h, a solution of tropinone (10.14g, 0.073 mol) in dry diethyl ether (60 ml) was added causing the reaction mixture to reflux. Reflux was maintained for a further 0.5 h, before the reaction mixture was allowed to cool. Water (40 ml) was then added and the reaction mixture was stirred for 0.25 h. The organic layer was then separated, dried (Na_2SO_4) and evaporated under reduced pressure to give a pale yellow oily solid, which was triturated with petroleum ether (60-80). The resultant suspension was then filtered to give the **title compound** as a white solid, which was dried *in vacuo* (9.04g, 50%).

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.32 (dd, 1H), 7.20 (m, 1H), 6.90 (m, 2H), 4.01 (s, 1H), 3.89 (s, 3H), 3.22 (m, 2H), 2.41 (m, 1H), 2.35 (s, 3H), 2.30 (m, 3H), 2.02 (m, 4H).

Description 8

3-(2-Methoxyphenyl)-8-methyl-8-azabicyclo[3.2.1]octane

The product from Description 7 (8.00g, 0.032 mol) was added slowly to trifluoroacetic acid (80 ml) with stirring and heated to reflux. After 11h, the reaction mixture was evaporated under reduced pressure and partitioned between 10% NaOH and CH_2Cl_2. The aqueous layer was then extracted with CH_2Cl_2 (2x) and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give a yellow oil which was dried *in vacuo*. The oil was redissolved in ethanol (100 ml) and was hydrogenated at atmospheric pressure in the presence of 10% PdC (1g) at 40° C. After 5 h, the reaction mixture was filtered through kieselguhr and the filter pad was washed with ethanol. The filtrate was then evaporated under reduced pressure to give the **title compound** as a yellow oil that crystallised on standing (6.68g, 90%).

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 7.21 (dd, 1H), 7.12 (dd, 1H), 6.92 (d, 1H), 6.80 (d, 1H), 3.80 (s, 3H), 3.40 (t, 1H), 3.30 (m, 2H), 2.48 (m, 2H), 2.30 (s, 3H), 2.10 (m, 2H), 1.48 (m, 4H).

Description 9

3-(2-Methoxyphenyl)-8-tert-butoxycarbonyl-8-azabicyclo[3.2.1] octane

3-(2-Methoxyphenyl)-8-methyl-8-azabicyclo[3.2.1]octane (D8, 6.66g, 0.029 mol) was dissolved in dichloromethane (200 ml) and was treated with 1-chloroethyl chloroformate (4.07 ml, 0.037 mol), followed by diisopropylethylamine (5.05 ml, 0.029 mol) with stirring at room temperature. After 20 h, the reaction mixture was evaporated under reduced pressure and the orange/brown oily residue was dried *in vacuo*. The oil was then redissolved in methanol (150 ml) and heated to reflux. After 0.5 h, the reaction mixture was allowed to cool and was evaporated under reduced pressure to give a brown oil. The oil was dried *in vacuo* and then redissolved in dichloromethane (100 ml). The resultant solution was then stirred at room temp. and triethylamine (4.50 ml, 0.032 mol) was added, followed by a solution of di-tert-butyl dicarbonate (6.96g, 0.032 mol) in dichloromethane (50 ml). After 2 h, the reaction mixture was washed with water (2X), dried (Na_2SO_4) and evaporated under reduced pressure to give a brown oil, which was purified by silica-gel

chromatography (1:1, petrol:diethyl ether) to give the **title compound** (8.84g, 100%) as a colourless oil that crystallised on standing.

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 7.12 (d, 2H), 6.90 (d, 1H), 6.82 (d, 1H), 4.28 (m, 2H), 3.80 (s, 3H), 3.02 (m, 1H), 2.45 (m, 2H), 2.05 (m, 2H), 1.65 (m, 2H), 1.52 (s, 9H), 1.48 (m, 2H).

Description 10

3-(5-Amino-2-methoxyphenyl)-8-tert-butoxycarbonyl-8-azabicyclo[3.2.1]octane

3-(2-Methoxyphenyl)-8-tert-butoxycarbonyl-8-azabicyclo[3.2.1]octane (D9, 4.40g, 0.014 mol) was dissolved in acetic anhydride (15 ml) and cooled to 0°C. Freshly ground copper (II) nitrate trihydrate (4.07g, 0.017 mol) was then added with stirring over 15 minutes. The reaction mixture was then allowed to warm to room temperature. After 1h, the reaction mixture was added slowly to an excess of sodium carbonate solution to give a pale blue suspension, which was extracted with dichloromethane (2x70 ml). The combined organic layers were then dried (Na_2SO_4) and evaporated under reduced pressure to give a brown oil which was partly purified by silica gel chromatography (2:1-1:1 petrol (60-80): Et_2O as eluant) to give a pale yellow oil (1.34g) which was redissolved in ethanol (50 ml) treated with 10% PdC (0.3g) and hydrogenated at atmospheric pressure at 35°C. After 5h, the reaction mixture was filtered through kieselguhr and the filter pad washed with ethanol. The filtrate was then evaporated under reduced pressure and the resultant brown oil was purified by silica-gel chromatography (3:1, petrol (60-80): Et_2O) to give the **title compound** as a brown oil (0.550g, 12%).

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 6.68 (d, 1H), 6.50 (m, 2H), 4.25 (m, 2H), 3.70 (s, 3H), 3.40 (s, 2H), 2.91 (m, 1H), 2.40 (m, 2H), 2.03 (m, 2H), 1.62 (m, 2H), 1.51 (s, 9H), 1.40 (m, 2H).

Description 11

3-(5-Amino-2-methoxyphenyl)-8-methyl-8-azabicyclo[3.2.1]octane

3-(5-Amino-2-methoxyphenyl)-8-tert-butoxycarbonyl-8-azabicyclo[3.2.1] octane (D10, 0.385g, 1.16 mmol) was dissolved in dry THF (30 ml) with stirring and was treated with lithium aluminium hydride (0.088g, 2.32 mmol) under argon. The reaction mixture was then heated to reflux. After 2 h and 4 h, further amounts of lithium aluminium hydride (0.132g, 3.48 mmol) were added. Reflux was then maintained for a further 4 h, before the

reaction mixture was allowed to cool. Water (0.352 ml) was then added, followed by 10% NaOH (0.528 ml) and water (0.880 ml). The mixture was then stirred for 0.5 h before being filtered through kieselguhr. The filter pad was then washed with THF (20 ml) and the filtrate evaporated under reduced pressure to give the **title compound** as a brown solid (0.242g, 85%).

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 6.65 (d, 1H), 6.58 (d, 1H), 6.48 (dd, 1H), 3.70 (s, 3H), 3.40 (s, 2H), 3.30 (m, 1H), 3.20 (m, 2H), 2.38 (m, 2H), 2.22 (s, 3H), 2.08 (m, 2H), 1.50 (m, 2H), 1.40 (m, 2H)

Description 12

N-[3-(8-tert-Butoxycarbonyl-8-azabicyclo[3.2.1]octan-3-yl)-4-methoxyphenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide

3-(5-Amino-2-methoxyphenyl)-8-tert-butoxycarbonyl-8-azabicyclo[3.2.1] octane (D10, 0.130g, 0.392 mmol) was transformed according to the method of Example 1 to give the **title compound** (0.202g, 85%) as a cream foam.

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.02 (s, 1H), 7.95 (m, 3H), 7.81 (s, 1H), 7.48 (m, 4H), 7.32 (d, 1H), 6.82 (d, 1H), 4.28 (m, 2H), 3.80 (s, 3H), 3.05 (m, 1H), 2.70 (s, 3H), 2.45 (m, 2H), 2.31 (s, 3H), 2.05 (m, 2H), 1.65 (m, 2H), 1.51 (s, 9H), 1.45 (m, 2H)

Description 13

6-Methoxy-7-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)quinoline

The product from description 11 (0.642g, 2.61 mmol) was treated with glycerol (0.360g, 3.91 mmol), and iodine (0.014g). Concentrated sulphuric acid (0.720g, 7.57 mmol) was then added dropwise with stirring. The reaction mixture was then heated to 190°C. After 2 h, the reaction mixture was allowed to cool and the resultant brown gum was dissolved in water and 10% sodium hydroxide solution was added until pH14 was reached. The resultant suspension was then extracted with chloroform (4x). The combined extracts were then dried (Na_2SO_4) and evaporated under reduced pressure to give a dark brown oil which was dried *in vacuo*. The oil was purified by silica-gel chromatography (100:20:1 CH_2Cl_2: MeOH:NH_3 as eluant) to give the **title compound** as a pale brown oil (0.453g, 62%)

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.71 (dd, 1H), 8.01 (d, 1H), 7.92 (s, 1H), 7.30 (dd, 1H), 7.0 (s, 1H), 3.90 (s, 3H), 3.55 (t, 1H), 3.30 (m, 2H), 2.53 (m, 2H), 2.30 (s, 3H), 2.12 (m, 2H), 1.58 (m, 4H).

Description 14

6-Methoxy-7-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl]-1,2,3,4-tetrahydroquinoline

The product from description 13 (0.443g, 1.57 mmol) was dissolved in ethanol (50 ml) and was treated with PtO_2 (0.1g). The resultant mixture was then hydrogenated at 50 psi. After 19h, the reaction mixture was filtered through kieselguhr. The filter pad was washed with ethanol and the filtrate evaporated under reduced pressure and dried *in vacuo* to give the **title compound** as a cream foam (0.44g, 98%).

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 6.50 (d, 2H), 3.72 (s, 3H), 3.60 (m, 2H), 3.48 (m, 1H), 3.22 (t, 2H), 2.70 (m, 4H), 2.60 (s, 3H), 2.20-1.85 (m, 9H).

Description 15

8-Methyl-3-trifluoromethylsulphonyloxy-8-azabicyclo[3.2.1]oct-2-ene

A stirred solution of tropinone (1.70g, 0.012 mol) in dry THF (20 ml) was cooled to -78°C under argon and was treated with a solution of LDA (2.0M in heptane/THF/ethylbenzene) (6.50 ml, 0.013 mol). After 1h, a solution of N-phenyltrifluoromethanesulphonimide (4.29g, 0.012 mol) in dry THF (15 ml) was added at -70°C. After addition was complete, the cooling bath was removed and the reaction mixture was allowed to warm to room temp. After a further 16h, the resulting pale yellow solution was evaporated under reduced pressure and dried *in vacuo* to give an orange oil. The oil was then purified by chromatography on neutral alumina (8.1 Petrol:EtOAc as eluant) to give the title compound as a yellow oil (2.34g, 72%).

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 5.82 (d, 1H), 3.47 (m, 2H), 2.82 (dd, 1H), 2.40 (s, 3H), 2.20-1.90 (m, 4H), 1.65 (m, 1H).

Description 16

8-Methyl-3-(3-nitrophenyl)-8-azabicyclo[3.2.1]oct-2-ene

8-Methyl-3-trifluoromethylsulphonyloxy-8-azabicyclo[3.2.1] oct-2-ene (D15) (0.400g, 1.48 mmol) was dissolved in DME (10 ml) and lithium chloride (0.188g, 4.44 mmol) was

added followed by 3-nitrobenzeneboronic acid (0.284g, 1.70 mmol), and 2M sodium carbonate solution (4 ml). Argon was then bubbled through the mixture and after 5 minutes $Pd(PPh_3)_4$ (0.086g, 0.074 mmol) was added. The mixture was then heated to reflux with stirring. After 4.5h the reaction mixture was allowed to cool and was left at room temp. for 12h, before being partitioned between chloroform and water. The aqueous layer was then extracted with chloroform (2X) and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give a brown oil that was dried *in vacuo*. The oil was purified by silica-gel chromatography (200:10.1, CH_2Cl_2MeOH:NH_3 as eluant) to give the title compound as a brown oil (0.147g, 46%).

^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 8.20 (t, 1H), 8.08 (dd, 1H), 7.70 (d, 1H), 7.50 (t, 1H), 6.42 (d, 1H), 3.52 (m, 2H), 2.95 (m, 2H), 2.49 (s, 3H), 2.30-2.00 (m, 2H), 1.95 (m, 1H), 1.62 (m, 1H).

Description 17
8-Methyl-3-(3-aminophenyl)-8-azabicyclo[3.2.1]octane

8-Methyl-3-(3-nitrophenyl)-8-azabicyclo[3.2.1]oct-2-ene (D16) (0.146g, 0.598 mmol) was dissolved in ethanol (25 ml) and was hydrogenated at atmospheric pressure in the presence of 10% PdC (0.1g) at 50°C. After 2h, the reaction mixture was allowed to cool to room temp. and hydrogenation was continued for a further 16h. The reaction mixture was then filtered through kieselguhr and the filter pad was washed with ethanol. The filtrate was then evaporated under reduced pressure to give the title compound as a pale yellow oil, which was dried *in vacuo* (0.104g, 81%).

^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.07 (t, 1H), 6.70 (d, 1H), 6.60 (s, 1H), 6.50 (dd, 1H), 3.65 (s, 2H), 3.33 (m, 2H), 3.00 (m, 1H), 2.50 (m, 2H), 2.38 (s, 3H), 2.05 (m, 2H), 1.75 (dd, 2H), 1.55 (d, 2H)

Example 1
N-[4-Methoxy-3-(1-methyl-4-piperidinyl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide

2'-Methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxylic acid (E.P. 0533268A1) (0.145g, 0.492 mmol) was suspended in CH_2Cl_2 (7ml) and was treated with oxalyl chloride (0.064 ml, 0.738 mmol), followed by a drop of dry DMF, with stirring. After 2h,

the reaction mixture was evaporated under reduced pressure to give the crude acid chloride as a pale yellow solid which was dried *in vacuo*. The crude acid chloride was then redissolved in dichloromethane (7 ml), triethylamine (0.068 ml, 0.492 mmol) was then added, followed by a solution of the product from description 3 (0.103g, 0.468 mmol) in dichloromethane (2 ml) and the mixture was stirred at room temperature for 4 h before being washed with sodium bicarbonate solution (1X). The organic layer was then dried (Na_2SO_4) and evaporated under reduced pressure to give a brown oil which was purified by silica-gel chromatography (7.5% MeOH/CH_2Cl_2 as eluant) and prep. t.l.c. (20% MeOH/EtOAc) to give the **title compound** as a pale yellow oil 10.072g, 30%, which was converted to its oxalate salt.

m.pt 180-182° C (oxalate salt)

^{1}H NMR (200 MHz, CD_3OD) δ (ppm) (oxalate salt): 8.06 (m, 3H), 7.97 (d, 1H), 7.62 (s, 1H), 7.52 (d, 3H), 7.40 (d, 1H), 7.02 (d, 1H), 3.89 (s, 3H), 3.62 (m, 2H), 3.20 (m, 3H), 2.92 (s, 3H), 2.70 (s, 3H), 2.39 (s, 3H), 2.10 (m, 4H).

Example 2

N-[4-Methoxy-3-(4-piperidinyl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide

The product from description 4 (0.200g, 0.394 mmol) was suspended in a mixture of 10% sodium hydroxide solution (35 ml), THF (30 ml), and methanol (30 ml), and heated to reflux with stirring. After 24 h the reaction mixture was concentrated under reduced pressure and the aqueous residue was extracted with chloroform (2X). The combined organic layers were then dried (Na_2SO_4) and evaporated under reduced pressure to give a colourless oil, which was purified by silica-gel chromatography (200: 10: 1 CH_2Cl_2: MeOH: NH_3 as eluant) to give the **title compound** as a white solid (0.050g, 26%) m.pt. 183-184° C (from $CHCl_3$/60-80 Petrol)

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.98 (m, 5H), 7.62 (dd, 1H), 7.49 (d, 2H), 7.38 (m, 2H), 6.90 (d, 1H), 3.82 (s, 3H), 3.15 (m, 3H), 2.80 (m, 2H), 2.70 (s, 3H), 2.30 (s, 3H), 2.05 (s, 1H), 1.82 (m, 2H), 1.62 (m, 2H).

Example 3

N-[4-Methoxy-3-(1-methyl-1,2,3,6-tetrahydropyrid-4-yl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide

The product from description 6 (0.090g, 0.189 mmol) was dissolved in ethanol (6 ml) and was treated with methyl iodide (0.047 ml, 0.756 mmol) with stirring and was heated to reflux. After 4 h and 8 h, further amounts of methyl iodide were added (0.047 ml, 0.756 mmol) and (0.094 ml, 1.512 mmol) respectively. After 24 h, the reaction mixture was allowed to cool and was concentrated to approximately half volume. The resultant yellow precipitate was then filtered off, and washed with diethyl ether to give the crude quaternary salt. The crude quaternary salt was then dissolved in a mixture of water (2 ml) and ethanol (2 ml), cooled to 0° C, and then treated with sodium borohydride (0.008g, 0.200 mol). After 0.25 and 0.5 h, further amounts of sodium borohydride (0.008g, 0.200 mmol) were added. The reaction mixture was treated with sodium hydrogen carbonate solution (10 ml), and water (10 ml). The resultant suspension was then extracted with chloroform (2 x 15 ml). The combined organic layers were then dried (Na_2SO_4) and evaporated under reduced pressure to give a colourless oil, which was purified by silica-gel chromatography (7.5% MeOH/CH_2Cl_2 as eluant) to give the **title compound** as a pale yellow oil (0.040g, 43%), which was converted to its oxalate salt.

m.pt. 192-194°C (oxalate salt)

^1H NMR (250 MHz, $CDCl_3$) (free base) δ (ppm): 7.95 (m, 4H), 7.85 (s, 1H), 7.63 (dd, 1H), 7.45 (d, 2H), 7.35 (m, 2H), 6.90 (d, 1H), 5.80 (s, 1H), 3.80 (s, 3H), 3.18 (m, 2H), 2.75-2.58 (m, 4H), 2.70 (s, 3H), 2.45 (s, 3H), 2.33 (s, 3H).

Example 4

N-[3-(8-Azabicyclo[3.2.1]octan-3-yl)-4-methoxyphenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide

The product from description 12 (0.194g, 0.319 mmol) was dissolved in dichloromethane (4 ml) and was treated with trifluoroacetic acid (2 ml) dropwise with stirring. After 20 h, the reaction mixture was evaporated under reduced pressure and the residue partitioned between sodium hydrogen carbonate solution and dichloromethane. The aqueous layer was extracted with dichloromethane (1X) and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the **title compound** as a yellow oil (0.160g, 99%) which was subsequently converted to its oxalate salt.

m.pt. 230-232° C (oxalate salt)

^{1}H NMR (400 MHz, CD_3SOCD_3) (oxalate salt) δ (ppm): 10.20 (s, 1H), 8.08 (d, 2H), 7.98 (s, 1H), 7.91 (d, 1H), 7.82 (s, 1H), 7.65 (dd, 1H), 7.58 (d, 2H), 7.42 (d, 1H), 7.00 (d, 1H), 4.20 (br s, 2H), 4.04 (s, 2H), 3.80 (s, 3H), 3.35 (m, 1H), 2.70 (s, 3H), 2.42 (m, 2H), 2.35 (s, 3H), 1.95 (m, 4H), 1.85 (m, 2H).

Example 5

N-[4-Methoxy-3-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide

3-(5-Amino-2-methoxyphenyl)-8-methyl-8-azabicyclo[3.2.1]octane (D11, 0.232g, 0.943 mmol) was transformed to give the **title compound** (0.184g, 38%) as a white foam according to the method outlined in Example 1. The title compound was subsequently converted to its oxalate salt.

m.pt. 218-219° C (oxalate salt)

^{1}H NMR (400 MHz, CD_3SOCD_3) (oxalate salt) δ (ppm): 10.20 (s, 1H), 8.05 (d, 2H), 7.98 (s, 1H), 7.90 (m, 2H), 7.65 (dd, 1H), 7.55 (d, 2H), 7.41 (d, 1H), 7.00 (d, 1H), 4.45 (br s, 1H), 3.85 (s, 2H), 3.80 (s, 3H), 3.33 (m, 1H), 2.68 (s, 6H), 2.55 (m, 2H), 2.32 (s, 3H), 2.15 (m, 2H), 1.98 (m, 4H)

Example 6

[3,4-Dihydro-6-methoxy-7-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-2H-quinolin-1-yl]-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methanone

The product from description 14 (0.440g, 1.54 mmol) was transformed to give the **title compound** (0.710g, 82%) as a cream foam according to the methodology described in example 1 and was subsequently converted to its oxalate salt.

m.pt. 140-143° C (oxalate salt)

^{1}H NMR (400 MHz, CD_3SOCD_3 at 80°C) (oxalate salt) δ(ppm): 7.92 (s, 1H), 7.88 (dd, 1H), 7.48 (d, 2H), 7.37 (d, 2H), 7.32 (d, 1H), 6.88 (s, 1H), 6.84 (s, 1H), 3.80 (m, 5H), 3.66 (m, 2H), 3.25 (m, 1H), 2.85 (t, 2H), 2.67 (s, 3H), 2.58 (s, 3H), 2.40-2.25 (m, 2H), 2.32 (s, 3H), 2.10-1.98 (m, 4H), 1.60 (m, 2H), 1.48 (dd, 2H)

Example 7

[7-(8-Azabicyclo[3.2.1]octan-3-yl)-3,4-dihydro-6-methoxy-2H-quinolin-1-yl]-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methanone

The product from example 6 (0.350g, 0.623 mmol) was dissolved in dichloromethane (15 ml) and was treated with 1-chloroethyl chloroformate (0.086 ml, 0.795 mmol), followed by diisopropylethylamine (0.138 ml, 0.795 mmol) with stirring under argon. After 20 h, the reaction mixture was evaporated under reduced pressure and the resulting brown foam was dissolved in methanol (20 ml), and heated to reflux with stirring. After 1h, the reaction mixture was evaporated under reduced pressure and the brown oily residue was purified by silica-gel chromatography (100:10:1 CH_2Cl_2: MeOH: NH_3 as eluant) to give the **title compound** as a pale yellow oil (0.201g, 59%), which was converted to its oxalate salt.

m.pt. 239-241° C (oxalate salt)

^{1}H NMR (250 MHz, $CDCl_3$) (free base) δ(ppm): 7.98 (s, 1H), 7.92 (d, 1H), 7.42 (d, 2H), 7.25 (m, 4H), 6.61 (s, 1H), 3.92 (t, 2H), 3.79 (s, 3H), 3.58 (m, 2H), 3.20 (m, 1H), 2.83 (t, 2H), 2.68 (s, 3H), 2.32 (s, 3H), 2.10 (m, 6H), 1.80 (m, 2H), 1.42 (m, 2H), 0.95 (s, 1H).

Example 8

N-[3-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide

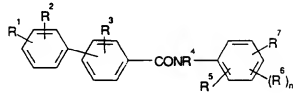
8-Methyl-3-(3-aminophenyl)-8-azabicyclo[3.2.1]octane (D17, 0.104g, 0.481 mmol) was transformed to give the title compound as a cream solid (0.130g, 55%) according to the method outlined in example 1, and was subsequently converted to its oxalate salt.

m.pt. 106-107°C (oxalate salt)

^{1}H NMR (250 MHz, $CDCl_3$) (free base) δ (ppm): 8.00 (m, 5H), 7.72 (s, 1H), 7.47 (m, 3H), 7.35 (m, 2H), 7.13 (d, 1H), 3.48 (s, 2H), 3.15 (m, 1H), 2.70 (s, 3H), 2.60 (m, 2H), 2.38 (s, 3H), 2.33 (s, 3H), 2.05 (m, 2H), 1.88 (dd, 2H), 1.60 (d, 2H).

CLAIMS:

1. A compound of formula (I) or a salt thereof:



(I)

in which

R^1 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, acyl, nitro, trifluoromethyl, cyano, SR^9, SOR^9, SO_2R^9, $SO_2NR^{10}R^{11}$, CO_2R^{10}, $NR^{10}SO_2R^{11}$, $CONR^{10}R^{11}$, $CO_2NR^{10}R^{11}$, $CONR^{10}(CH_2)_aCO_2R^{11}$, $(CH_2)_aNR^{10}R^{11}$, $(CH_2)_aCONR^{10}R^{11}$, $(CH_2)_aNR^{10}COR^{11}$, $(CH_2)_aCO_2C_{1-6}$alkyl, $CO_2(CH_2)_aOR^{10}$, $CONHNR^{10}R^{11}$, $NR^{10}R^{11}$, $NR^{10}CO_2R^{11}$, $NR^{10}CO(CH_2)_aNR^{10}R^{11}$, $NR^{10}CONR^{10}R^{11}$, CR^{10}=NOR^{11}, CNR^{10}=NOR^{11}, where R^9, R^{10} and R^{11} are independently hydrogen or C_{1-6}alkyl and a is 1 to 4 or R^1 is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur;

R^2 and R^3 are independently hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, C_{1-6}alkylOC_{1-6}alkyl, acyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano, CO_2R^{10}, $CONR^{10}R^{11}$, $NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen or C_{1-6}alkyl;

R^4 is hydrogen or C_{1-6}alkyl and R^5 is hydrogen, halogen, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy or R^4 and R^5 together form a group -A- where A is $(CR^{12}R^{13})_q$ where q is 2, 3 or 4 and R^{12} and R^{13} are independently hydrogen or C_{1-6}alkyl or A is $(CR^{12}R^{13})_r$-D where r is 0, 1, 2 or 3 and D is oxygen, sulphur or CR^{12}=CR^{13};

R^6 is hydrogen, halogen, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy;

n is 1 or 2; and

R^7 is an optionally substituted 5 to 7-membered saturated or partially saturated heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen or sulphur or R^7 is an optionally substituted 6,6 or 6,5 bicyclic ring containing a nitrogen atom and optionally a further heteroatom selected from from oxygen, nitrogen or sulphur.

2. A compound according to claim 1 in which R^1 is oxadiazolyl.

3. A compound according to claim 2 or 3 in which R^2 is C_{1-6}alkyl.

4. A compound according to any one of claims 1 to 3 in which R^3 is hydrogen.

5. A compound according to any one of claims 1 to 4 in which R^4 and R^5 are both hydrogen or R^4 with R^5 forms an ethyl or propyl group.

6. A compound according to any one of claims 1 to 5 in which R^6 is C_{1-6}alkoxy.

7. A compound according to any one of claims 1 to 6 in which R^7 is a piperidine, tetrahydropyridine, tropane or isoquinuclidine ring.

8. A compound according to claim 1 which is:

N-[4-Methoxy-3-(1-methyl-4-piperidinyl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,

N-[4-Methoxy-3-(4-piperidinyl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,

N-[4-Methoxy-3-(1-methyl-1,2,3,6-tetrahydropyrid-4-yl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,

N-[3-(8-Azabicyclo[3.2.1]octan-3-yl)-4-methoxyphenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,

N-[4-Methoxy-3-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,

[3,4-Dihydro-6-methoxy-7-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-2H-quinolin-1-yl]-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methanone,

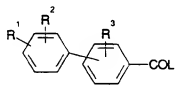
[7-(8-Azabicyclo[3.2.1]octan-3-yl)-3,4-dihydro-6-methoxy-2H-quinolin-1-yl]-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methanone,

N-[3-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,

or a pharmaceutically acceptable salt thereof.

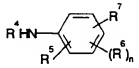
9. A process for the preparation of a compound of formula (I) which comprises

(a) for compounds where R^4 is hydrogen or C_{1-6}alkyl and R^5 is hydrogen, halogen, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy, reaction of a compound of formula (II):



(II)

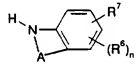
in which R^1, R^2 and R^3 are as defined in formula (I) and L is a leaving group, with a compound of formula (III):



(III)

in which R^4 and R^5 are as defined above and R^6, R^7 and n are as defined in formula (I); or

(b) for compounds where R^4 together with R^5 forms a group A, reaction of a compound of formula (II) as defined above with a compound of formula (IV):



(IV)

in which A is as defined above and R^6, R^7 and n are as defined in formula (I);

and optionally after (a) or (b) and in any order:

- converting a compound of formula (I) into another compound of formula (I)
- forming a pharmaceutically acceptable salt.

10. A compound according to any one of claims 1 to 7 for use in therapy.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 96/01465

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D451/02 C07D271/06 A61K31/46 A61K31/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J.MED.CHEM., vol. 37, no. 15, 22 July 1994, WASHINGTON, pages 2253-2257, XP002008422 CLITHEROW,J.W. ET AL.: "Evolution of a Novel Series of [(N,N-Dimethylamino)propyl]- and Piperazinylbenzanilides as the First Selective 5-HT1D Antagonists" * see page 2255, Table 2, compounds 9 - 11 * see the whole document ---	1-10
X	WO,A,94 15920 (GLAXO GROUP LTD ;CARTER MALCOLM (GB)) 21 July 1994 * overlap of main claims * see the whole document ---	1-10
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 July 1996	16.08.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stellmach, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 533 268 (GLAXO GROUP LTD) 24 March 1993 cited in the application * overlap of main claims * see the whole document	1-10
X	EP,A,0 533 266 (GLAXO GROUP LTD) 24 March 1993 cited in the application * overlap of main claims * see the whole document	1-10
X	WO,A,95 04729 (SMITHKLINE BEECHAM PLC ;DUCKWORTH DAVID MALCOLM (GB); JENKINS SARA) 16 February 1995 * overlap of main claims * see the whole document	1-10
X	WO,A,95 06637 (SMITHKLINE BEECHAM PLC ;GASTER LARAMIE MARY (GB); DUCKWORTH DAVID) 9 March 1995 * overlap of main claims * see the whole document	1-10
X	WO,A,95 06644 (SMITHKLINE BEECHAM PLC ;DUCKWORTH DAVID MALCOLM (GB); GASTER LARAM) 9 March 1995 see the whole document	1-10
X	GB,A,2 276 162 (GLAXO GROUP LTD) 21 September 1994 see the whole document	1-10
Y	EP,A,0 533 267 (GLAXO GROUP LTD) 24 March 1993 cited in the application see the whole document	1-10
Y	GB,A,2 273 930 (GLAXO GROUP LTD) 6 July 1994 see the whole document	1-10
Y	WO,A,95 06044 (SMITHKLINE BEECHAM PLC ;DUCKWORTH DAVID MALCOLM (GB); GASTER LARAM) 2 March 1995 see the whole document	1-10
Y	GB,A,2 276 160 (GLAXO GROUP LTD) 21 September 1994 cited in the application see the whole document	1-10

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO,A,95 26328 (SMITHKLINE BEECHAM PLC ;GASTER LARAMIE MARY (GB); WYMAN PAUL ADRIA) 5 October 1995 see the whole document ---	1-10
P,X	WO,A,96 06079 (SMITHKLINE BEECHAM PLC ;GASTER LARAMIE MARY (GB)) 29 February 1996 see the whole document -----	1-10

2

INTERNATIONAL SEARCH REPORT

Int tional application No.
PCT/EP 96/01465

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims No.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Formula I in claim 1 contains only a minor fixed part, which is not sufficiently limited by claims 2-7. Considering the large number of variables, the scope of said claims cannot be evaluated and an exhaustive search is not possible. Claims 1-7, 9-10 have been searched incompletely.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No
PCT/EP 96/01465

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9415920	21-07-94	AU-B- 5815594	15-08-94
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		AU-B- 656021	19-01-95
		AU-B- 2453092	25-03-93
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		JP-A- 6116251	26-04-94
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		NO-A- 940974	17-03-94
		US-A- 5358948	25-10-94

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No
PCT/EP 96/01465

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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WO-A-9506044	02-03-95	EP-A- 0714389	05-06-96
GB-A-2276160	21-09-94	NONE	
WO-A-9526328	05-10-95	NONE	
WO-A-9606079	29-02-96	NONE	